REMARKS

1. Claims

Prior to the present amendment, claims 3 and 10-15 are pending in the application, and claims 4-9 are cancelled.

Claim 3 has been amended by insertion of the term "and wherein said administration is by subcutaneous administration." The basis for the amendment can be found throughout the specification and particularly for example on page 5, paragraph [0050].

Claim 15 has been amended by deletion of the terms "nephropathy, retinopathy". The basis for the amendment can be found throughout the specification and particularly for example on page 2, paragraph [0019].

The Amendment and cancellation of the claims are not to be construed as acquiescence to any of the objections/rejections set forth in the instant office action, and were done solely to expedite prosecution of the application. No new matter has been inserted. Applicants reserve the right to pursue the claims as originally filed or similar claims, in this or one or more subsequent patent applications.

Entry of these amendments is requested under 37 CFR 1.116 because they will place the case in condition for allowance or in better form for appeal. Based on the amendment and following remarks, Applicants respectfully request that the Examiner reconsider the outstanding rejections and that they be withdrawn.

1. Withdrawal of Certain Rejections.

Applicants acknowledge the withdrawal of the previous rejection of claim 14 under 35 U.S.C. §112 second paragraph. Applicants also acknowledge the withdrawal of the previous rejections of claims 3, 10,13,& 15 under 35 U.S.C. §103 in view of Ido et al., (Science 277 563-566, 1997); and of claim 12 in view of Ido et al., and Johansson et al., (Diabetologia 39 687-695, 1996); and of claim 11 over Ido et al., in view of Wahren et al., (WO1998/013384) and Johansson et al., (BBRC 295(5) 1045-1040 2002).

2. Supplemental IDS

Applicants respectively request that the Examiner provides a signed acknowledgement of the references provided by the applicant in the previous response and form 1449 which was provided with the last response.

3. Petition for Request for Withdrawal of Finality of the last Office Action

Applicants herewith include a petition under 37 CFR 1.181 for reconsideration and withdrawal of the finality of the rejection of the last office action based on fact that the amendments introduced into the

claims did not necessitate the new art rejection because they did not substantially change the scope of the claims in question, and the fact that the new rejections were not based on information submitted in an information disclosure statement filed by applicants.

4. Rejection of claims 3, 10, & 12-15 Under 35 U.S.C. § 102(b).

The Examiner rejects claims 3, 10, & 12-15 under 35 USC 102(b) as being unpatentable over Johansson et al., (Diabetologia (1992) 35 121-128). Specifically the Examiner is of the opinion that because the terms "rate-controlling agents", "continuous administration" and "prolonged period of time" are not explicitly defined in the specification, and "absence specific guidance within the disclosure, the claim is interpreted as encompassing a once daily administration, by any mode other than osmotic pump and excluding infusions that go beyond the bounds of 24 hours ("daily" of the claims)." (See present Office Action, paragraph 7). Accordingly the Examiner concludes that the claims fail to distinguish over Johansson et al.

Applicants respectfully traverse the assertion that the claimed invention is anticipated by Johansson et al.

The currently pending claims are directed to a method of treating diabetes and/or microvascular diabetic complications comprising administering C-peptide or a pharmaceutical composition comprising C-peptide to a patient once daily, wherein said once daily administration does not include a continuous administration, or the presence of release rate-controlling agents. The claims are further directed to a C-peptide fragment, EGSLQ; wherein said patient is a human; wherein said C-peptide is an aqueous solution, and wherein said complication are diabetic nephropathy, retinopathy or neuropathy.

The amendments to claims 3 and 15, if entered, would introduce the additional limitation "wherein said administration is by subcutaneous administration" into claim 3, and limit claim 15 to diabetic neuropathy.

Applicants' note, that as provided in the MPEP at 2106, "Office personnel must rely on the applicant's disclosure to properly determine the meaning of terms used in the claims. Marman v. Westview Instruments, 52 F.3d 967, 980, 34 USPQ2d 1321, 1330 (Fed. Cir.)(en banc), aff'd, US., 116 S. Ct. 1384 (1996). An applicant is entitled to be his or her own lexicographer, and in many instances will provide an explicit definition for certain terms used in the claims. Where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim."

Accordingly, the definitions of "once daily administration" and "continuous administration" provided in the specification controls the correct interpretation of these terms. Specifically the specification includes the following definitions:

> "[0025] Reference to a "once daily dose" or "once daily administration" means, of course, not only that the medication itself is only given once per day ***but that the patient receives no other C-peptide treatment.*** Such instructions may be made clear by the prescribing physician and/or in literature accompanying the packaged medication... "(Emphasis added) (See instant specification, pages 2 & 3 paragraph [0025]).
>
> "..A once daily dose does not cover a continuous administration and is distinct therefrom. A once daily dose hence is directed to only one administration per day of the C-peptide treatment whereas a continuous administration would be constantly administering C-peptide treatment, ***or administering it over a prolonged period of time."*** (Emphasis added)." (See instant specification, pages 2 & 3 paragraph [0025]).

As stated in the MPEP at 2106, "If an applicant does not define a term in the specification, that term will be given its "common meaning". Paulsen, at 30 F. 3d 1480, 31 USPQ2d at 1674. "

Specifically in the context of the claimed invention, and consistent with its common meaning, the term "prolonged" refers to an administration of C-peptide, that occurs for any period of time that is longer than the time required for a single administration of C-peptide, such as a single s.c. Injection. To interpret the term in any other way would be inconsistent with the instant specification, or the common meaning of the term "prolonged".

As stated in the MPEP 2106. "Office personnel are to give claims their broadest reasonable interpretation ***in light of the supporting disclosure***. See, e.g., In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989)." (Emphasis added)

Specifically the instant specification provides the following disclosure on page 2, paragraph [0012]:

> "C-peptide is known to have a relatively short half-life. In humans, the half-life is approximately 30 minutes and a dose of C-peptide injected into a rat would be expected to have disappeared entirely from circulation within 2-3 hours."
>
> "The inventors of the present application have now surprisingly found that C-Peptide given in a once daily dose can be used to treat diabetes and particularly type 1 diabetes, and diabetic complications effectively. This is particularly surprising since ***a once daily administration of C-peptide would be expected to leave an animal without detectable C-peptide levels for at least 18-20 hours per day (approximately 75-80 % of the time).*** (Emphasis added)

Thus the specification teaches that the administration of a once daily dose of C-peptide would be expected to lead to circulating C-peptide levels that would be below detectable levels for at least 75-80 % of the time, and thus by definition the actual once daily administration of C-peptide to the patient must occur over a period of administration that is significantly less than 75-80% of the day (after taking into account the time required for the dose to decay to below the level of detection).

Accordingly the Examiner's conclusion that the claimed method of once daily administration also includes infusions that provide continuous administration of C-peptide for up to almost an entire 24 hour period is in complete contradiction to the teaching in the instant specification, and definitions of the terms "once daily administration" and "continuous administration".

By contrast to the Examiners analysis of Johansson et al., this reference neither teaches nor suggests once daily administration as defined and claimed in the instant invention.

In fact, Johansson et al., actually teaches **the prolonged administration of <u>two</u> distinct doses** of C-peptide to the subjects in one day; a high C-peptide dose, and a low C-peptide dose; see for example Johansson et al., page 121 Summary of invention:

> "After baseline measurements C-peptide was **<u>infused during two periods</u>** of 60 min at rates of 5 and 30 pmol.kg^{-1}. min^{-1}." Johansson et al., Page 121 (Summary) left hand column, lines 9-12. (Emphasis added).

See also Johansson et al., page 122-123 (Subjects and methods).

> "In Group 1, C-peptide was given i.v. for 1 h (low dose, bolus of 25 pmol.kg^{-1}.min.$^{-1}$ for 1.5 min followed by 10 pmol.kg^{-1}. min^{-1} for 6.5 min **<u>and ending with</u>** 5 pmol.kg^{-1}.min^{-1} for 52 min) **<u>and then for an additional hour</u>** using a bolus and infusion rates **<u>six times those of the first infusion period</u>** (high dose)". (Emphasis added).

As reiterated again below, this administration of more than one dose of C-peptide per day, is clearly outside the scope of the instant claims:

> "[0025] Reference to a "once daily dose" or "once daily administration" means, of course, not only that the medication itself is only given once per day ***but that the patient receives no other C-peptide treatment.*** Such instructions may be made clear by the prescribing physician and/or in literature accompanying the packaged medication... "(Emphasis added) (See instant specification, pages 2 & 3 paragraph [0025]).

Accordingly because Johansson et al., actually teaches the administration of at least two doses of C-peptide, rather than a single daily administration of C-peptide, as defined in the specification, and reiterated above, it cannot anticipate claims 3, 10, & 12-15, either prior to, or after entry of the instant amendment.

Secondly, and as discussed above, the correct meaning of "continuous administration" as defined in the specification, includes not only continuous administration over, or exceeding, the entire 24 hour period as recognized by the Examiner, but in addition also excludes C-peptide that is *administered over a prolonged period of time.*

Consistent with the definitions listed above, the description in the instant specification clearly provides that once daily administration of the invention **does not encompass the prolonged** administration of C-peptide, i.e. those that extend the period of administration of C-peptide beyond a

single, once daily administration. Specifically, for example, prolonged I.V. infusions over several hours as taught by Johansson et al., are excluded from the term "once daily administration."

Accordingly because Johansson et al., clearly describes the prolonged I.V. administration of C-peptide, this reference does not teach a single daily administration of C-peptide, as this term is defined in the specification, and therefore it cannot anticipate claims 3, 10, & 12-15, either prior to, or after entry of the instant amendment.

Finally Johansson et al., teaches only that the short term administration of C-peptide for a single day may exert a short term regulatory influence on renal function and stimulate glucose utilization in Type 1 diabetics. (See for example Johansson et al. page 127, right hand column, last six lines).

Johansson et al., neither teaches nor suggests a once daily therapeutic regimen as currently described and claimed to treat diabetes and /or diabetic complications, and Johansson et al., neither described, nor recognized a long term beneficial effect of once daily administration of C-peptide to effectively treat diabetes and /or diabetic complications.

By contrast, the present applicants discovery that a single daily dose is as effective as the administration of multiple daily doses (e.g. 3-4 times daily), or continuous administration, over a sustained period of time as shown in Example 1 of the instant specification, is an extremely important and unexpected advance in the treatment of the microvascular complications of diabetes, compared to the prior art methods of multiple dosing and continuous administration of C-peptide.

Indeed the present application is based on a previously unrecognized property of C-peptide which overcomes the problem of the administration of multiple daily doses, or continuous or prolonged infusions. As discussed on page 5, third paragraph of the instant application, it was accepted wisdom that a once daily dose of C-peptide would have left an animal without detectable C-peptide levels for at least 18-20 hours of the day because the short biological half life of C-peptide would result in the rapid decay of circulating levels of C-peptide within the animal. Thus there is no reason to believe that once daily dosing would be effectively able to treat diabetes or diabetic microvascular complications because the circulating concentrations of C-peptide would be below its therapeutic window for the vast majority of time.

While Johansson et al. showed short term effects of C-peptide on renal function when this was *continuously administered by IV infusion*, there is no reasonable expectation of success that based on these short term effects that the use of a single daily administration, *as that term is defined*, would be effective to treat diabetes or the complications of diabetes, such as renal nephropathy.

As discussed previously, the ability of C-peptide to be able to treat the microvascular complications of diabetes when provided only once a day in view of its known half life of about 30 minutes is in complete contrast to the teachings of the prior art, and contrary to accepted wisdom because

the prior art as a whole suggests that because of the C-peptide's short biological half life, it is necessary to provide prolonged continuous infusion, or multiple subcutaneous injections in order to maintain the peptide within its therapeutic window.

More specifically there was no reasonable expectation of success based on the teaching of Johansson et al., that once daily administration of C-peptide would be effective for the treatment of diabetic microvascular diabetic complications. In fact, as stated above, Johansson et al., clearly does not teach once daily administration as currently claimed at all.

Accordingly because Johansson et al., does not teach, nor suggest once daily administration, as this term is defined in the instant specification, it cannot anticipate claims 3, 10, & 12-15, either prior to, or after entry of the instant amendment. Accordingly Applicants respectfully requests that the rejection of these claims under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

5. Rejection of claim 11 Under 35 U.S.C. § 103(a).

The Examiner rejects claim 11 under 35 USC § 103(a) as being unpatentable over Johansson et al., in view Wahren et al., WO/1998/013384 ("Wahren et al."). Specifically the Examiner is of the opinion that "One of ordinary skill in the art would recognize the use of the EGSLQ pentapeptide fragment, equivalent to claimed SEQ ID NO:2, taught by Wahren et al. in the method of Johansson et al. A skilled artisan would be motivated to combine the prior art elements because this specific fragment maintains the stimulatory activity and thus would result in the predictable effect of treating diabetic renal nephropathy."

Applicants respectfully traverse the rejection and submit that the combination of references would not put one of ordinary skill in the art in possession of the claimed invention, nor would one of ordinary skill in the art have any expectation of success in making the claimed invention based on the combination of references.

The Johansson et al reference is discussed above, and there is nothing in Wahren et al., either alone or in combination that would make up for the deficiencies of the Johansson et al., reference. Again, there is nothing in Johansson et al., or the teachings of the prior art, that provides an expectation of success that once daily administration of C-peptide, (as defined and claimed) would be therapeutically effective given the short biological half life of the C-peptide.

Accordingly the combination of references does not put one of ordinary skill in the art in possession of the claimed invention, and the Examiner has not established a prima facie case of

obviousness with respect to claim 11. Accordingly Applicants respectfully requests that the rejection of claim 11 under 35 U.S.C. § 103 be reconsidered and withdrawn.

6. **Conclusion**

As discussed above, the discovery that a single daily does is as effective as the administration of multiple daily doses (e.g. 3-4 times daily), or continuous administration is an extremely important and unexpected advance in the treatment of the microvascular complications of diabetes.

This view was also shared by the International Examiner who indicated in the International Preliminary Report on Patentability that "C-peptide is known to have a relatively short half life. Due to the short half life of C-peptide, prior art discloses several days doses, a continuously administered dose or delayed release formulations. However, the inventors of the present application have surprisingly found that C-peptide given in a once daily dose can be used to treat diabetes (even in the absence of any release rate controlling agents or continuous administration). The prior art does not provide any indication that would prompt the skilled person to use a C-peptide formulation (without any release rate controlling agents or continuous administration) as a medicament for once daily administration for the treatment of diabetes."

In view of the above remarks, reconsideration and allowance of the application are respectfully requested.

The Commissioner is authorized to charge any additional fees that may be required in connection with this submission, including petition fees and extension of time fees, or to credit any overpayments to Deposit Account No. 50-4297.

Respectfully submitted,

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